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Letters to the editor

A syndrome of overgrowth and acromegaloidism with normal growth hormone secretion is associated with chromosome 11 pericentric inversion

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Introduction

- Top
- Introduction
- Case report
- Discussion
- References

An acromegalic phenotype in late childhood or early adulthood is shared by a variety of clinical conditions, including growth hormone (GH) excess.[1] Exclusion of an abnormality of the somatotrophic axis in a young patient with acromegaloid features should lead the differential diagnosis towards diagnoses such as pachydermoperiostosis (MIM 167100[2])[3-5] or insulin mediated pseudoacromegaly, a disorder associated with severe insulin resistance.[6] In the absence of insulin resistance and findings characteristic of pachydermoperiostosis, such as thickening of the periosteum (visible mostly in skull *x* rays) or the skin, acrolysis, or alopecia,[4 5 7] another genetic syndrome associated with acromegaloid features may be considered.[8-13] These are rare conditions, having each been described in individual kindreds, and their causes remain unknown. Inheritance, when present, appears to be as an autosomal dominant trait. They are almost always associated with abnormalities of the skin, the mucosa, and its appendages, such as keratitis,[9] thickened mucosa,[10] hypertrichosis,[12] and cutis verticis gyrata.[8 13]

In this report, we identify a chromosomal anomaly that was confirmed by fluorescence in situ hybridisation (FISH) in a patient with acromegaloid features and his family. The patient, his mother, and sibs participated in protocol 97-CH-0076 (National Institute of Child Health and Human Development, National Institutes of Health (NIH)) and consented to cytogenetic and DNA studies, and the use of the proband's photographs for the purposes of medical education and publication.

Case report

Top
Introduction
Case report
Discussion
References

The proband was a 14 year 3 month old male (fig 1) who was referred to our clinic with the diagnosis of possible acromegaly. He was born at term after an uncomplicated pregnancy. His birth weight was 5018 g (over the 95th centile for a newborn and on the 50th centile for a 21/2 month old boy), and his length was 60 cm (over the 95th centile for a newborn and on the 50th centile for a 3 month old boy). At birth, he had a submucosal cleft palate and a diaphragmatic hernia for which he underwent surgical repair. Later, as a child, he developed sleep apnoea, but the rest of his health and development were normal. He entered and completed puberty normally and continued to grow in parallel to but above the 95th centile. The patient's mother, one sib, and an uncle (who had died of complications of sleep apnoea) had palatal clefts, overgrowth, and acromegaloid features of variable severity (fig 2).

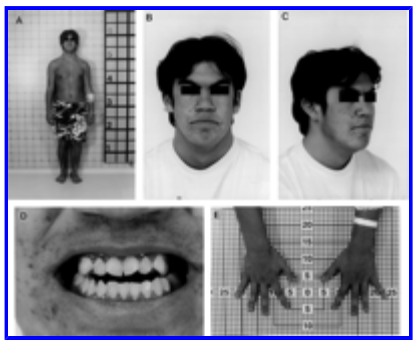

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Figure 1 Clinical findings in the patient: (A) Symmetrical overgrowth. (B) Acromegaloid facies. (C) Lack of prognathism despite coarse facies and prominent supraorbital ridges.(D) Normally spaced teeth. (E, F) Absence of acral enlargement.

Figure 2 Pedigree and clinical information on members of the family with acromegaloidism and inv(11)(p15.3;q23.3).

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The patient's physical examination showed symmetrical overgrowth (both height and weight over the 95th centile); his facies and body habitus were acromegaloid but the patient had normal tooth spacing and an absence of acral enlargement (fig 1). The function and size of the lacrimal glands were normal. Oral examination showed a normally sized tongue. The size of the submandibular salivary glands was normal on examination of the neck. Thyroid, heart, and abdominal examinations were normal with no evidence of nodules, cardiac dysfunction, or organomegaly, respectively. The skin texture was normal, albeit somewhat oily; the patient had acne, as shown in fig 1B. Genital examination and pubic hair were normal (Tanner V); testicular volume was 25-30 ml, bilaterally.

The evaluation of the patient's somatotrophic axis is presented in table 1. All assays were performed at Endocrine Sciences (Calabassas Hills, CA) or Covance Laboratories (Vienna, VA). It included responses to both stimulation (arginine, clonidine, and L-Dopa) and suppression (oral glucose tolerance test (oGTT)) tests of GH, thyrotrophin releasing hormone (TRH) stimulation testing, and insulin-like growth factor type 1 (IGF-1) levels. The patient's 24 hour, every 20 minute GH secretion pattern was also obtained (data not shown). Radiological and skin biopsy examinations were also performed to exclude pachydermoperiostosis. Pituitary imaging and sonograms of the abdomen, liver, kidneys, and testes (data not shown) were also obtained. During the patient's evaluation at the NIH, his bone age was estimated; it was then compared with previous recordings of the patient's bone age at different chronological ages, obtained elsewhere (table 2).

Table 1 Clinical profile of the proband

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Table 2 Bone versus chronological age in the proband

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The patient lacked the characteristic for acromegaly mandibular and acral enlargements (fig 1), but he had prominent supraorbital ridges and generally coarse facies. His laboratory evaluations, including oGTT, TRH stimulation, 24 hour GH secretion, and IGF-1 levels, were normal (table 1). Pituitary magnetic resonance and other imaging studies, which included an echocardiogram and renal ultrasonography, were also normal (data not shown). The patient did, however, have an advanced bone age (table 2). The clinical information that was available for the other members of the family is summarised in fig 2.

To search for features of pachydermoperiostosis, radiological imaging of the skull and the extremities and a skin biopsy were obtained. The former showed normal bones, without any signs of periosteal proliferation or new bone growth; the fingers were normal, without any widening indicative of clubbing (data not shown). A biopsy of skin obtained from the left forearm showed normal histology (data not shown). Adnexal structures were of the expected number and size (hair follicles and eccrine glands). Furthermore, the mucin content in this biopsy did not differ from normal controls.[4]

The patient's mother and sisters were also briefly examined, although they declined further investigation. The mother and one of the sisters had a height in excess of the 95% centile. Both shared cleft palate defects with the proband but had less obvious acromegaloid features. The mother's GH, GHRH, and IGF-I levels and oGTT responses were also normal (data not shown).

High resolution karyotype analysis was obtained by standard methods from the patient, his mother, father, and three sisters. Probes for fluorescence in situ hybridisation (FISH) were nick translated and hybridised on metaphase chromosomes that were prepared from peripheral lymphocytes, as previously described.[14-16] Ten metaphases were scored for every probe examined. The commercially available probe for the *MLL* gene at 11q23[17] was labelled with digoxigenin (Oncor Inc, Gaithesburg, MD) and detected with fluorescein (Oncor, Gaithesburg, MD). Chromosome identification was accomplished through cohybridisation with a chromosome 11 telomere specific probe (11pter) that was labelled with Spectrum Green (Vysis, Naperville, IL). Images were obtained with a Zeiss Axiophot microscope, equipped with a "Cytovision" imaging system (Applied Imaging, Pittsburgh, PA), as previously described.[16]

The peripheral blood karyotype of the proband showed that, on one of the chromosome 11 pair, the chromatin near the tip of the p arm had a pattern similar to that of the distal 11q region (fig 2), suggesting a pericentric inversion of chromosome 11 or a 46,XY,inv(11)(p15.3;q23.3) karyotype. FISH with two probes that hybridise to the 11p telomere (11pter) and to the *MLL* gene on 11q23,[17] respectively, showed that, on one chromosome 11, the two probes were positioned on the p arm, with the *MLL* probe centromeric to the 11pter probe; the two probes hybridised to their expected positions (11pter on the distal p arm and *MLL* on the distal q arm) on the other chromosome 11 (fig 4). Classical and molecular cytogenetic analysis showed the same abnormality in the patient's mother and one of his

sisters (data not shown); these studies were normal in the patient's father and his other two sisters, none of whom had this phenotype.

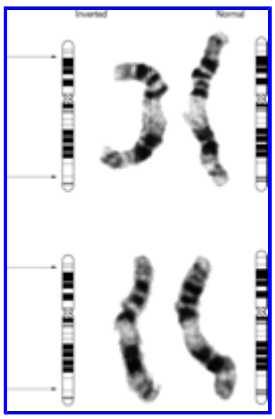

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Figure 3 G banding high resolution karyotype of the proband; the arrows point to two paradigms of the inv(11)(p15.3;q23.3) abnormality.

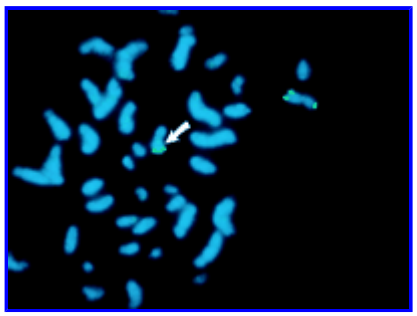

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Figure 4 FISH on cultured lymphocytes from the proband with two probes that hybridise to the 11p telomere (11pter) and to the MLL gene on 11q23, respectively, showed that, on one chromosome 11, the two probes were positioned proximal to each other (indicated by the arrow), whereas they hybridised to their expected positions on the other chromosome 11 (upper right corner of the picture).

Discussion

Top
Introduction
Case report
Discussion
References

No chromosomal abnormality or genetic locus has previously been described in the various syndromes associated with acromegaloidism. The present report identified a pericentric inversion of chromosome 11 that segregated with acromegaloid features and other abnormalities in one family. This finding may assist in the identification of gene(s) responsible for these conditions, only after proper clinical classification of acromegaloidism.

Acromegaloidism describes a highly heterogeneous group of disorders. In general, acromegaly and

gigantism, the two syndromes of GH excess, share several features with pseudoacromegaly caused by severe insulin resistance.[6] The distinction between these two groups of disorders is made by the laboratory finding of insulin resistance in pseudoacromegaly.[6] Pachydermoperiostosis and the other syndromes associated with acromegaloidism have neither insulin resistance nor GH excess, the exception being an apparently coincidental GH producing pituitary adenoma found in a patient with pachydermoperiostosis.[18]

The differentiation of pachydermoperiostosis from the other conditions is made radiologically or histologically or both. Patients with this condition have evidence of periosteal thickening of the skull or the long bones, digital clubbing, and/or acrolysis, similar to that seen in hypertrophic pulmonary osteoarthropathy or inherited acropathy.[3 4 7 19] In addition, several cutaneous findings, including papular mucinosis, hyperkeratosis, and generalised hypertrophy of epidermal appendages,[3 5 7 8] are distinctive features suggestive of pachydermoperiostosis. Cutis verticis gyrata (multiple furrows on the scalp and/or forehead) is also often seen in association with pachydermoperiostosis.[4 19] Periostosis without acromegaloid features or any skin involvement has been reported and is referred to as Currarino disease[20]; however, this condition should not be considered in the differential diagnosis of acromegaloid syndromes.

Other reports of families with an acromegaloid phenotype include a Kirghizian family with arthritis, osteolysis, keratitis, and other ectodermal findings with autosomal recessive inheritance (MIM 221810),[9] a Canadian family with thickened oral mucosa and acral hyperextensibility (MIM 102150),[10] and an Irish kindred with coarse facies and generalised hypertrichosis since childhood.[12] The family reported by Dallapicola *et al*[11] was similar to the one reported by Hughes *et al*.[10] As in most of the other patients with non-pachydermoperiostosis acromegaloid syndromes,[9-12] the features of acromegaly in our family were confined to the face. On the other hand, the proband had a history of a cleft palate and a diaphragmatic hernia. Neither of these congenital anomalies has been reported in other patients with acromegaloid syndromes. Although the diaphragmatic defect was not present in any of the patient's affected relatives, variable cleft palate was present in all of them.

The aetiology of acromegaloidism in our family remains unclear. The overgrowth and advanced bone age of the proband support the notion of aberrant expression of an unknown growth factor. The presence of an unidentified growth factor in the serum of patients with acromegaloidism has been suggested before.[21] A substance of approximate molecular weight of 70 000 daltons was found in the sera of five subjects with acromegaloid features. Its growth promoting activity was shown by determining its effect on human erythroid cell progenitors in vitro. It was shown to be independent of epidermal, nerve, or fibroblast growth factors and growth hormone.[21] Although the present study could be used to suggest that perhaps the gene coding for this factor is on chromosome 11, the patients studied by Ashcraft *et al*[21] had phenotypes different from those of our patients; at least one of them had acral thickening similar to that seen in acromegaly or pseudoacromegaly and another had, perhaps, true acromegaly.[21]

It is also possible that the genetic defect in our kindred is not a growth factor per se, but rather a signalling molecule that participates in a related pathway. It was recently found, for example, that patients with insulin resistance and pseudoacromegaly[6] have a defect in phosphoinositide 3-kinase

signalling,[22] [23] leading to insulin resistance and activation of mitogenic pathways stimulated by the insulin receptor.[22]

The genetic defect responsible for the phenotype in our family could also involve inappropriate repression of a gene because of fusion of genetic material from another sequence on chromosome 11, the interruption of an inhibitory state (imprinting or a related state), or the deletion of suppressive elements. Similar abnormalities have been described in patients with chromosome 11 cytogenetic defects that involved growth factors and other genes mapped to this chromosome[24] and would also explain the variability of the phenotype seen in our family. Examples include Beckwith-Wiedemann syndrome that maps to 11p15.5 and is believed to result from relaxation of imprinting of this area leading to IGF type 2 (IGF-2) overexpression.[24] The 11p15.3 breakpoint of the pericentric chromosomal inversion in our kindred, however, is quite distal to the IGF-II and related loci.[25] [26] A search of the available databases[27] failed to find any other imprinted sequences or known growth factor genes that map to the breakpoints of the inversion.

In conclusion, we present a family with variable clinical expression of acromegaloidism associated with other developmental defects that segregate with a pericentric inversion of chromosome 11. This report may lead to the identification of new gene(s) on chromosome 11 that are important for midline fusion and growth of facial structures.

Acknowledgments

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References

Top
Introduction
Case report
Discussion
References

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